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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,993	11/24/2003	Michele Cargill	CL001496	3651

25748 7590 11/06/2006

CELERA GENOMICS
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EXAMINER	
SWITZER, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,993	CARGILL ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *7-20 and 23-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,21 and 22* is/are rejected.

7)☒ Claim(s) *1-6,21 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/5/05*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20061026*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, Claims 1-6, 21-22, further electing with traverse polymorphism HCV8227677, as represented in SEQ ID NO: 7368 in the paper filed 8/24/06 is acknowledged.

The response asserts 10 nucleotide sequence should be examined together based upon MPEP Section 803.04. This argument has been thoroughly reviewed but not deemed persuasive because the MPEP provides for up to 10 sequences to be examined. First, it is noted that the claims are not drawn to nucleotide sequences, but to methods for detecting Alzheimer's disease by detecting a single nucleotide polymorphism within a sequence. The search for such an invention involves not only a sequence search of a particular SEQ ID NO but also a search of the patent and non-patent literature to determine if a particular position within the SEQ ID NO is known to have a polymorphism within a population, and also if that polymorphism is associated with Alzheimer's disease. This search requires more than a sequence search but also a review of relevant patent and non-patent literature that discusses the gene, it's structure and polymorphisms within the gene. Often, this information is found embedded in literature within tables and figures, and is it is frequently not represented in sequence databases or even within abstracts of papers. Further, while the MPEP is permissive of the examination of additional sequences, the MPEP does not set forth a requirement that the examination of additional sequences be undertaken when a restriction is otherwise proper. Each of the instant methods which require detecting SNPs are patentably distinct and require an undue burden to search and consider together. The resources required to search 10 sequences has dramatically increased

since the 1996 OG notice. The volume of data within the databases has grown exponentially. It is no longer reasonable for a search of 10 sequences to be performed in a single application. Moreover, as noted, the instant search does not rely solely on the computer resources, but requires a search for SNPs within a gene. Many genes have more than one name and the number of polymorphisms within the gene must be individually searched for novelty. An article which teaches polymorphisms within a gene does not necessarily use the same numbering system, or the same nomenclature as the instant application. Many papers disclose SNPs within Tables that are not easily searchable and require burden to analyze the contents of tables within an article which have not been indexed in any comprehensive database. Therefore, a search of methods for detection of multiples SNPs in the alternative in a single application is an undue burden on the office. The requirement is still deemed proper and is therefore made FINAL.

It is noted that in the instant application, the elected SNP is referred to as both hCV8227677 and hCV26838632 (see specification page 22), and that instant SEQ ID NO: 7368 is identical to instant SEQ ID NO: 962. There is no restriction requirement between these two identical sequences which disclose the same exact information.

Applicant is correct that the inclusion of claim 23 in group VI in the restriction requirement was a typographical error, and that it is claims 24 and 34 that the examiner intended to include in this restriction group (see page numbered 2 of the response filed 8/24/06).

2. Claims 7-20 and 23-35 are withdrawn from prosecution as being drawn to a non-elected invention.

3. Claims 1-6 and 21-22 are objected to for specifically reciting non-elected subject matter. Cancellation of this subject matter will be required prior to any possible allowance of the claims.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 21 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by WANG (US 2003/0204075 A9).

Wang teaches using SNP probes to classify people according to their genetic variation, wherein the SNP probes can discriminate between alleles of a SNP nucleic acid in a conventional allelic discrimination assay (¶ 0020 and 0021, for example). One of the polymorphisms taught by Wang is identical to the instantly elected polymorphism. Namely, nucleotides 395-595 of SEQ ID NO: 5 taught by Wang (US 2003/0204075) are identical to instant SEQ ID NO: 7368, including the indication of a C/T polymorphism at position 495 of the sequence taught by Wang (this position aligns with instant position 101 of SEQ ID NO: 7368). Thus, Wang provides a method for detecting a SNP in a nucleic acid molecule which comprises contacting a test sample with a reagent which specifically hybridizes to a SNP in SEQ ID NO: 7368 and detecting the formation of a hybridization complex, using allele-specific probe hybridization.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-6 and 21-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to any single nucleotide polymorphism in SEQ ID NO: 7368. SEQ ID NO: 7368 is 200 base pairs in length. The specification teaches a single polymorphism at position 101.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

With respect to claims which encompass polymorphisms, as provided in Example 11, no common structural attributes identify the members of the genus. The current claims encompass a large genus of polymorphisms which encompass SNPs in SEQ ID NO: 7368. This large genus is represented in the specification by only the particularly named polymorphism for which data is provided. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SNPs of SEQ ID NO: 7368 alone is insufficient to describe the genus. There is no description of the mutational sites that exist in nature and there is no description of how the structure of SEQ ID NO: 7368 relates to the structure of any strictly neutral alleles. The general knowledge in the art concerning variants does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes are not described. The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms. The polymorphisms shown are not representative of the genus of any polymorphism. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6 and 21-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-6 are drawn to a method for identifying an individual who has an altered risk for developing Alzheimer's disease by detecting a SNP in SEQ ID NO: 7368 in said individual's nucleic acids wherein the presence of the SNP is correlated with altered risk for Alzheimer's disease. Thus the nature of the claimed invention requires the knowledge of a reliable association between alleles of a single nucleotide polymorphism present in SEQ ID NO: 7368 and altered risk for developing Alzheimer's disease. Claims 20-21 do not specifically set forth

the relationship between the SNP and Alzheimer's disease, but the use of the claimed method would require the knowledge of a relationship between the SNP and some phenotype, and the only suggested phenotype in the specification is Alzheimer's disease.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

Wang teaches the polymorphism elected for prosecution, namely, nucleotides 395-595 of SEQ ID NO: 5 taught by Wang (US 2003/0204075) are identical to instant SEQ ID NO: 7368, including the indication of a C/T polymorphism at position 495 of the sequence taught by Wang (this position aligns with instant position 101 of SEQ ID NO: 7368).

Further, the art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility. Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population

diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Indeed, the unpredictability of the instantly claimed invention is specifically discussed in the post-filing date references of Bertram et al. (The American Journal of Human Genetics, Volume 79, pages 180-183) and Minster et al. (Neuroscience Letters 408(206) 170-172). In both of these references, the relationship set forth in the instant claims, namely between a polymorphism at position 101 of SEQ ID NO: 7368 and an altered likelihood of developing Alzheimer's disease were unable to be replicated. Further, it is noteworthy any association suggested by the data in Bertram et al. suggest that the opposite allele is related to disease (Bertram et al., p. 180). In response to the Bertram et al. paper, Grupe et al. (authorship including two of the instant inventors) state that "Further replication in well-characterized sample sets is required to assess whether the association is genuine (p. 184, Grupe et al. The American Journal of Human Genetics, Vol. 79, pages 183-184).

Thus, even given the data in the specification, due to the highly unpredictable nature of this technology area, it remains highly unpredictable whether or not a reliable association exists between the polymorphism at position 101 of SEQ ID NO: 7368 and risk for Alzheimer's disease.

Guidance in the Specification.

The specification provides no evidence that any polymorphisms within SEQ ID NO: 7368 is reliably associated with any risk for developing Alzheimer's disease.

The specification teaches a case-control genetic study to determine the association of a large set of SNP in the human genome with late onset Alzheimer's disease (Example beginning on page 117). The data suggest a putative relationship between the hCV8227677 SNP and late onset Alzheimer's disease in humans (see Table 6, page 5 of 6), however, in view of the high level of unpredictability in this technology area, these data are not sufficient to support the notion

that there is a reliable association between alleles of this SNP and risk for Alzheimer's disease in humans.

The specification does not provide guidance for detecting a SEQ ID NO: 7368 SNP in "any" individual, only humans. Individual encompasses any human, dog, cat, mouse, ferret, gorilla, for example. The specification and the art do not provide any guidance that the polymorphic SNP is present in other animals or individuals. The specification appears to be directed to persons, i.e. humans. It is unpredictable other animals will have SEQ ID NO: 7368, the SNP and that the SNP is associated with Alzheimer's disease. Without further undue and unpredictable experimentation to determine whether the association is present over a range of individuals, a method for associating the SNP with a disease in any individual in unpredictable and undue.

The specification does not provide guidance for detecting any SNP within SEQ ID NO: 7368. The specification teaches a single SNP location in SEQ ID NO: 7368 at position 101. It is unpredictable that there are any other SNPs in SEQ ID NO: 7368 and the location of the SNPs if there are SNPs. Further the skilled artisan would be required to perform detailed analysis on each other position of SEQ ID NO: 7368 to determine if there is a polymorphism at the location and whether the polymorphism is associated with Alzheimer's disease. This experimentation is unpredictable and would require undue trial and error experimentation.

The specification does not appear to teach what the increased risk is compared to. As provided in Claims 2 and 4 of the instant application, the claim requires increased risk or decreased risk, but does not provide what the increase or decrease is in relation to. Increase and decrease in the abstract are relative terms.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied prior to being able to practice the claimed invention as broadly as written. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the unpredictability of associating polymorphisms with disease, and in particular the hCV8227677 polymorphism with Alzheimer's disease, it is unpredictable any polymorphisms is associated with altered risk any Alzheimer's disease in any individual. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties of association. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

8. Claims 1-6 are free of the prior art.

The prior art teaches a polymorphism at position 101 of instant SEQ ID NO: 7368. For example, nucleotides 395-595 of SEQ ID NO: 5 taught by Wang (US 2003/0204075) are identical to instant SEQ ID NO: 7368, including the indication of a C/T polymorphism at position 495 of the sequence taught by Wang (this position aligns with instant position 101 of SEQ ID NO: 7368). There is no teaching or suggesting in the prior art that this polymorphism can be used as in indicator for altered risk for developing Alzheimer's disease. At best, Wang et al. provide a invitation to investigate a potential relationship between this polymorphism (or any of the almost hundred and fifty thousand polymorphism disclosed by Wang) and any possible human disease, but there is no expectation of success given the high level of unpredictability and the empirical nature of the prior art area of establishing a relationship between a phenotype and a genotype.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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Juliet C. Switzer
Primary Examiner
Art Unit 1634

October 31, 2006